

Claims

We Claim:

- 546 C1*
1. A method for diagnosing, or determining a predisposition to developing, an arterial wall disruptive disorder in a subject, comprising detecting one or more genotypic or phenotypic markers for macular degeneration in the eye, wherein said marker is indicative of arterial wall disruptive disorder or of a predisposition to developing arterial wall disruptive disorder.
 2. The method of claim 1, wherein said arterial wall disruptive disorder is selected from the group consisting of: an aortic aneurysm, a peripheral aneurysm, a visceral aneurysm, and an intracranial aneurysm.
 3. The method of claim 1, wherein said arterial wall disruptive disorder is a dissecting aneurysm.
 4. The method of claim 2, wherein said aortic aneurysm is an abdominal aortic aneurysm (AAA).
 5. The method of claim 2, wherein said aortic aneurysm is a thoracic aortic aneurysm (TAA).
 6. The method of claim 1, wherein said macular degeneration is age-related macular degeneration (AMD).
 7. The method of claim 1, wherein said macular degeneration is the exudative or neovascular (wet) form, which is characterized by disciform scars and/or choroidal neovascularization (DS/CNV) or an exudative precursor phenotype.
 8. The method of claim 1, wherein said marker includes the presence of drusen in the subretinal pigmented epithelial (sub RPE) space.
 9. The method of claim 1, wherein said marker includes one or more drusen-associated markers.
 10. The method of claim 9, wherein said drusen-associated marker is selected from the group consisting of immunoglobulins, amyloid A ($\alpha 1$ amyloid A), amyloid P component, C5 and C5b-9 terminal complexes, HLA-DR, fibrinogen, Factor X, and prothrombin, complements 3, 5 and 9, complement reactive protein (CRP), immunoglobulin lambda and kappa light chains, Factor X, HLA-DR, apolipoprotein A, apolipoprotein E, antichymotrypsin, $\beta 2$ microglobulin, factor X, fibrinogen, prothrombin, thrombospondin, elastin, collagen,

Sub B1

LFA1

alpha,

vitronectin, ICAM-1, LFA1, LFA3, B7, IL-1, IL-6, IL-12, TNF- α , GM-CSF, heat shock proteins, colony stimulating factors (GM-CSF, M-CSFs), TNF α , and IL-10.

Sub B2

5 11. The method of any one of claims 1 or 9, wherein said marker is detected using at least one technique selected from the group consisting of fundus fluorescein angiography (FFA), fundus photography (FP), electroretinogram (ERG), electrooculogram (EOG), visual fields, scanning laser ophthalmoscopy (SLO), visual acuity measurements and dark adaptation measurements.

Sub B2

10 12. The method of claim 9, wherein said drusen-associated marker is a phenotypic marker is selected from the group consisting of RPE cell death or dysfunction, immune mediated events, dendritic cell proliferation, migration, differentiation, maturation and activation in the sub RPE space, the presence of disciform scars, the presence of choroidal neovascularization and/or the presence of choroidal fibrosis.

Sub B2

15 13. The method of claim 12, wherein RPE cell death or dysfunction is detected by detecting expression of a gene selected from the group consisting of HLA-DR, CD68, vitronectin, apolipoprotein E, clusterin and S-100.

Sub B2

20 14. The method of claim 12, wherein said immune mediated event may be detected by detecting an auto-antibody, detecting choroidal dendritic cells, detecting accumulation of leukocytes in the choroid, detecting an increase in HLA-DR immunoreactivity of retinal microglia, detecting an increase in the synthesis of type VI collagen and detecting an up-regulation of an immune-associated molecule.

Sub B2

25 15. The method of claim 14, wherein said auto-antibody is an antibody directed against drusen, RPE, or a retinal antigen.

Sub B2

16. The method of claim 14, wherein said immune-associated molecule which is selected from the group consisting of immunoglobulins, complement, complement receptors, chemokines, cytokines, CD antigens, MHC antigens, acute phase reactants, proteases, protease inhibitors, immune complexes, and antigens.

Sub B2

17. The method of claim 12, wherein dendritic cell maturation and proliferation is detected by detecting GM-CSF, IL-4, IL-3, SCF, FLT-3 and TNF α .

Sub B2

30 18. The method of claim 12, wherein said migration and differentiation in the sub RPE space may be detected by determining the presence and/or level of a dendritic cell marker or combination of markers is selected from the group consisting of CD1a, CD4, CD14, CD68,

*Sub
B4*

CD45, CD83, CD86 and S-100.

19. The method of claim 12, wherein said fibrosis in said macula may be detected by determining the presence or level of elastin, fragments of elastin, collagen, or fragments of collagen.

5 20. The method of claim 12, wherein said fibrosis in said macula may be detected by examining the expression of at least one marker selected from the group consisting of elastin, fibrillin-2, PI-1, PI-2, b-1 integrin, emilin, fibulins, collagens, ficolin, HME, MMPs, TIMPs, lammin, Big H3, lysyl oxidases, LTLPs, PLOD, vitronectin, MFAP-1 and MFAP-2.

10 21. The method of claim 9, wherein said drusen-associated marker is a genotypic marker selected from the group consisting of HLA-DR, CD68, vitronectin, apolipoprotein E, clusterin and S-100, heat shock protein 70, death protein, proteasome, Cu/Zn superoxide dismutase, cathepsins, and death adaptor protein RAIDD.

15 22. A method for diagnosing, or determining a predisposition to, arterial wall disruptive disorder in a subject, comprising:

- (a) isolating a nucleic acid from a subject, and
(b) genotyping said nucleic acid;

wherein at least one allele from a macular degeneration-associated haplotype is predictive of an increased risk of arterial wall disruptive disorder.

20 23. A method for diagnosing, or determining a predisposition to, arterial wall disruptive disorder in a subject, said subject having family members diagnosed with macular degeneration, comprising:

- a) isolating a nucleic acid from a subject;

amplifying the nucleic acid with primers which amplify a region of a chromosome corresponding to a polymorphic marker for macular degeneration; and

25 c) analyzing the amplification product

wherein the presence of a polymorphism indicative of an allele type linked to macular degeneration is indicative of an allele type linked to arterial wall disruptive disorder or a predisposition for developing arterial wall disruptive disorder.

24. A method for diagnosing, or determining a predisposition to, arterial wall disruptive

said subject diagnosed with
disorder in a subject, said subject having family members diagnosed with a macular degeneration, comprising:

- (i) isolating a genomic nucleic acid from a subject;
- (ii) amplifying short tandem repeat sequences in said genomic DNA to obtain a genotype;
- (iii) comparing said genotype to the genotype of known DNA sequences to detect nucleotide sequence polymorphisms; and
- (iv) determining the presence or absence of a polymorphism in the genomic DNA of said subject;

wherein the presence of a polymorphism indicative of an allele type linked to macular degeneration is indicative of an allele type linked to arterial wall disruptive disorder or a predisposition for developing arterial wall disruptive disorder.

26. The method of any one of claims 22, 23, or 24, wherein said genotype substantially corresponds to a region of the short arm of human chromosome 2, said region being bordered by marker D2S2352 and D2S1364.

26. The method of any one of claims 22, 23, or 24, wherein said genotype substantially corresponds to a region of a chromosome selected from the group consisting of 1p21-q13, 1q25-q31, 2p16, 6p21.2-cen, 6p21.1, 6q, 6q11-q15, 6q14-q16.2, 6q25-q26, 7p21-p15, 7q31.3-32, not 8q24, 11p12-q13, 13q34, 16p12.1, 17p, 17p13-p12, 17q, 18q21.1-q21.3, 19q13.3, 22q12.1-q13.2 and Xp11.4.

27. The method of any one of claims 22, 23, or 24, wherein said subject is a mammal.

28. The method of claim 27, wherein said subject is a human.

29. The method of any one of claims any one of claims 22, 23, or 24, wherein said wherein said arterial wall disruptive disorder is selected from the group consisting of: an aortic aneurysm, a peripheral aneurysm, a visceral aneurysm, and an intracranial aneurysm.

30. The method of any one of claims 22, 23, or 24, wherein said arterial wall disruptive disorder is a dissecting aneurysm.

31. The method of claim 29, wherein said aortic aneurysm is an AAA.

32. The method of claim 29, wherein said aortic aneurysm is a TAA.

- any one*
- said macular*
33. The method of ~~any one~~ of claims 22, 23, or 24, wherein said macular degeneration is AMD.
34. The method of any one of claims 22, 23, or 24, wherein said macular degeneration contains disciform scars and choroidal neovascularization (DS/CNV).
- 5 35. A kit for diagnosing arterial wall disruptive disorder, comprising:
- a) primers for amplifying a region of a chromosome having a polymorphism indicative of macular degeneration;
 - b) reagents for performing DNA amplification; and
 - c) reagents for analyzing the amplified nucleic acid.
- 10 36. A method for diagnosing, or detecting a predisposition to developing, an arterial wall disruptive disorder in a subject, comprising performing an immunoassay on a sample obtained from said subject using an antibody specific for a gene product indicative of macular degeneration, wherein detection of the presence of bound antibody indicates that the subject has macular degeneration or a predisposition to developing macular degeneration and therefore has an arterial wall disruptive disorder or a predisposition for developing an arterial wall disruptive disorder.
- 15 37. A kit for diagnosing, or detecting a predisposition to developing, an arterial wall disruptive disorder, comprising reagents for performing the immunoassay of claim 36.
- 20 38. A method for treating or preventing the development of arterial wall disruptive disorder in a subject, comprising administering to a subject a pharmaceutically effective amount of a macular degeneration therapeutic.
39. The method of claim 38, wherein said macular degeneration therapeutic is an anti-inflammatory agent.
- 25 40. The method of claim 38, wherein said anti-inflammatory agent is an antagonists of TNF- α , IL-1, GM-CSF, IL-4 and IL
41. The method of claim 38, wherein said macular degeneration therapeutic is IL-10, M-CSF, IL-6 and IL
42. The method of claim 38, wherein said macular degeneration therapeutic is an inhibitor

of the expression of one or more DRAMs.

43. The method of claim 38, wherein said DRAM is selected from the group consisting of amyloid A protein, amyloid P component, antichymotrypsin, apolipoprotein E, β 2 microglobulin, complement 3, complement C5, complement C5b-9 terminal complexes, factor X, fibrinogen, immunoglobulins (kappa and lambda), prothrombin, thrombospondin and vitronectin.
44. A pharmaceutical composition useful for treating or preventing arterial wall disruptive disorder, comprising an effective amount of a macular degeneration therapeutic and a therapeutically acceptable carrier.
- 10 45. The method of claim 38, wherein said arterial wall disruptive disorder is an aortic aneurysm.
46. The method of claim 45, wherein said aortic aneurysm is an AAA.
47. The method of claim 45, wherein said aortic aneurysm is a TAA.
48. The method of claim 38, wherein said macular degeneration is AMD.
- 15 49. The method of claim 38, wherein said macular degeneration contains disciform scars and choroidal neovascularization (DS/CNV).
50. A method for identifying an agent for, or determining the efficacy of, an agent for treating or preventing arterial wall disruptive disorder in a subject, comprising:
- 20 (1) administering to a subject an agent at a non-toxic dosage; and
(2) determining whether drusen formation or neovascularization is inhibited or has resolved.
51. A method for identifying an agent for treating or preventing arterial wall disruptive disorder in a subject, comprising:
- 25 (a) contacting a non-human model for macular degeneration with an agent; and
(b) monitoring one or more markers of macular degeneration,
wherein the absence or disappearance of one or more of said markers is indicative of the inhibition of arterial wall disruptive disorder.
52. The method of any one of claims 50 or 51, wherein said arterial wall disruptive disorder

is an aortic aneurysm.

53. The method of claim 52, wherein said aortic aneurysm is AAA.
54. The method of claim 52, wherein said aortic aneurysm is TAA
- 5 55. The method of any one of claims 50 or 51, wherein said macular degeneration is AMD.
56. The method of any one of claims 50 or 51, wherein said macular degeneration contains disciform scars and choroidal neovascularization (DS/CNV).
57. The method of any one of claims 50 or 51, wherein said marker is the presence of drusen in the subretinal pigmented epithelial (sub RPE) space.
- 10 58. The method of any one of claims 50 or 51, wherein said marker is one or more drusen-associated molecules (DRAMs).
59. The method of claim 58, wherein said DRAM is selected from the group consisting of amyloid A protein, amyloid P component, antichymotrypsin, apolipoprotein E, β 2 microglobulin, complement 3, complement C5, complement C5b-9 terminal complexes, factor X, fibrinogen, immunoglobulins (kappa and lambda), prothrombin, thrombospondin and vitronectin.
- 20 60. An animal model for arterial wall disruptive disorder comprising an animal which has or is predisposed for developing macular degeneration, wherein the presence of, severity of, or predisposition for macular degeneration in said animal is indicative of the presence of, severity of, or predisposition for arterial wall disruptive disorder.
61. The animal of claim 60, wherein said animal is a transgenic animal.
62. The animal of claim 61, wherein said animal has been treated to develop macular degeneration.
- 25 63. An animal model for arterial wall disruptive disorder comprising a transgenic animal which carries a genetically modified homolog of a human AMD-associated gene.
64. The animal model of claim 61, wherein the human AMD-associated gene is a gene

chromosomal

consisting

within a human ~~chromosomal~~ locus selected from the group consisting of: 1p21-q13, 1q25-q31, 6p21.2-cen, 6q, 6q14-q16.2, 7p21-p15, 7q31.3-32, 8q24, 11p12-q13, 13q34, 16p12.1, 17p, 17p13-p12, 17q, 18q21.1-q21.3, 19q13.3, 22q12.1-q13.2, and Xp11.4.

5 65. An animal model for arterial wall disruptive disorder comprising a transgenic animal which carries a genetically modified drusen-associated marker gene.

10 66. The animal model of claim 65, wherein the drusen-associated marker gene is selected from the group consisting of: immunoglobulins, amyloid A (α 1 amyloid A), amyloid P component, C5 and C5b-9 terminal complexes, HLA-DR, fibrinogen, Factor X, and prothrombin, complements 3, 5 and 9, complement reactive protein (CRP), immunoglobulin lambda and kappa light chains, Factor X, HLA-DR, apolipoprotein A, apolipoprotein E, antichymotrypsin, β 2 microglobulin, factor X, fibrinogen, prothrombin, thrombospondin, elastin, collagen, vitronectin, ICAM-1, LFA1, LFA3, B7, IL-1, IL-6, IL-12, TNF-alpha, GM-CSF, heat shock proteins, colony stimulating factors (GM-CSF, M-CSFs), TNF α , IL-10, HLA-DR, CD68, vitronectin, apolipoprotein E, clusterin, S-100, death protein, heat shock protein 70, proteasome, Cu/Zn superoxide dismutase, cathepsins, death adaptor protein RAIDD, Ig mu, Ig lambda, Ig J, Ig kappa chains, CD1a, CD4, CD14, CD68, CD83, CD86, CD45, PECAM, MMP14, ubiquitin, FGF, IL-1, IL-6, IL-12, TNF-alpha, and GM-CSF.

15 20 67. A kit for diagnosing arterial wall disruptive disorder comprising at least two antibodies selected from the group consisting of: an anti-elastin antibody, and anti-collagen antibody, an anti-chemokine antibody, and anti-vitronectin antibody.

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